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Date: July 6, 2000

Case Docket No. BJA 170A

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Inventor(s): Wolfgang Neuberger, Stefan Spaniol

For: Active Endoscopic Photodynamic Therapy Devices; Systems and Method

Enclosed are:

(✓) Patent Application
(✓) 3 Sheets of Drawings
(✓) Information Disclosure Statement - included in Specification
(✓) Combined Declaration and Power of Attorney
(✓) Copies of Prior Art References
(✓) PTO ~~1449~~ SB/08A
(✓) Assignment of the Invention to; **CeramOptec Industries, Inc.**
(✓) Small Entity Status Declaration
(✓) Certificate of Mailing (Express)
(✓) PTO 1619
(✓) Check No 21487 in the amount of $385.00 to cover the filing and recording fees.

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Appendix E

Applicant or Patentee: WOLFGANG NEUBERBER STEFAN SPANIOL
Serial No. or Patent No.: _____ Docket No.: BJA170A
Filed or Issued: _____
For: ACTIVE ENDOSCOPIC PHOTODYNAMIC THERAPY DEVICES

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9 (f) AND 1.27 (b)) - INDEPENDENT INVENTOR

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9 (c) for purpose of paying reduced fees under section 41 (a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled:
"ACTIVE ENDOSCOPIC PHOTODYNAMIC THERAPY DEVICES", described in

( ) the specification filed herewith
( ) application serial no. _____, filed _____
( ) patent no. _____, issued _____.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9 (c) if that person had made the invention, or to any concern under 37 CFR 1.9 (d) or a non-profit organization under 38 CFR 1.9 (e).

I have not assigned, granted, conveyed or licensed nor am I under any obligation under contract of law to assign, grant, convey or license any rights in this invention to any person, concern or organization which would not qualify as a small business concern under 37 CFR 1.9 (d) or a non-profit organization under 37 CFR 1.9 (e).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate (37 CFR 1.28 (b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which verified statement is directed

Name of Inventor	Name of Inventor	Name of Inventor
WOLFGANG NEUBERGER	STEFAN SPANIOL	
Signature of Inventor	Signature of Inventor	Signature of Inventor
Date	Date	Date
5th June 2000	5th June 2000	

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The undersigned hereby certifies that this document was delivered to the United States Post Office in East Longmeadow, Massachusetts 01028 between 9:00 a.m. and 6:00 p.m. as EXPRESS MAIL on July 6, 2000. The undersigned further declares that this Certification is made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under applicable sections of United States law and that willful false statements made before the United States Patent and Trademark Office may jeopardize the validity of the application or of issuing patents related thereto.

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Active Endoscopic PhotoDynamic Therapy Devices; Systems and Method

Inventor(s): Wolfgang Neuberger

Stefan Spaniol

Assignee: CeramOptec Industries Inc.

Background of the Invention

1. Field of the invention

The present invention relates to medical endoscopic devices, and optoelectronics and in particular a diffuse electromagnetic radiation system located at the distal end of the endoscopic device useful for PhotoDynamic Therapy(PDT).

2. Invention Disclosure Statement

PDT generally relies on exposing a presensitized area to a selected wavelength of activating radiation. The activating radiation typically comes from a diode laser. A diffuse source of radiation can expose a greater area to activation energy and therefore necrotize a larger area. A diffuse light in the human body has conventionally been created with a diffuser or other such attachment to the distal end of an optical fiber. (e.g. U.S. Pat. Nos. 5,431,647; 5,429,635; 5,363,458). The power and light source are both external which requires that the transmission fiber be coupled to the source. The process and mechanisms of coupling often results in a loss of the energy emitted by the source. Therefore, these devices are prone to a loss of efficiency due to coupling problems. Once transmitted, the emitting light from the fiber possesses a narrow NA, limited dispersion and a single axial component. To compensate the light must be diffused with a diffuser. The diffuse light created by these scattering glasses is limited by the characteristics of light travelling through the delivery fiber and it is prone to problems such as uneven distribution of light and hotspots.

Endoscopic devices require coupling an electromagnetic radiation source to a fiber so that the radiation may be brought to the desired treatment area. Examples of these devices are the laser endoscopes found in U.S. Pat. Nos. 4,589,404; 5,135,534; 5,540,676. The process of coupling the fiber to the source generally results in a loss of

efficiency and power. Also, coupling usually changes the characteristics of the irradiated light from the source. The resultant emission from the fiber is a beam with a small NA, high coherency, and narrow coverage area. The application of PDT with current technology is often a laborious process due to the limited treatment area created by the fiber. A diffuse electromagnetic source ideally would be able to treat a larger area.

An endoscopic device which does place a radiation source at the distal end of the device, is demonstrated in U.S. Pat. No. 5,468,238. The referenced device places a single diode laser at the distal end to maintain spatial coherency and to reduce the loss of power; however, this device is limited in application. If applied for PDT purposes, a narrow light source makes the procedure slow and inefficient. The source of the light is limited to the single diode and therefore is limited to a single wavelength. Flexibility in the types of sources would create broader applicability for a device.

Another device is demonstrated in U.S. Pat. No. 4,852,567. This laser tipped catheter solves the problem of wavelength transmission limitations in silica fibers. By placing a laser crystal at the distal end of the catheter, electromagnetic radiation of one wavelength of light may be converted to another more desired wavelength which is not transmittable through silica fibers. This system still places the initial power source external to the end of the catheter and will suffer from a loss of power due to coupling. The main focus of this invention is the conversion of wavelengths of one radiation source to a different wavelength which a normal optical fiber could not transmit. This invention does not create a diffuse light source. The placement of a laser crystal at the distal end of the fiber does not suggest placement of an actual electromagnetic source at the end of an endoscopic device. This system also limits the area of PDT application due to the narrowly emitted beam.

It would be useful and more efficient to have a source, which provides evenly diffuse radiation and can irradiate a broad area with diffuse radiation. It would also be useful to have a radiation source at the distal end of the endoscopic device to increase efficiency and control. It would be additionally useful to place multiple light sources at the distal end to have the possibility of multiple wavelengths and a greater consistency to

the light. The utility of these features would be further increased by circumventing the transmission limitations of fiber optics. The prior art contains only limited solutions to some of these problems. The present invention addresses all these problems.

Brief Summary and Objectives of the Invention

It is an object of the present invention to provide an endoscopic system which has a diffuse source of electromagnetic radiation at the distal end of the device suitable for broader treatment areas in such applications as PDT.

It is another object of the present invention to provide a system which can utilize a wide range of illumination options not limited to laser technology.

Briefly stated the present invention provides an active endoscopic system which contains an electromagnetic radiation means located at the distal end of the endoscopic device allowing for variable intensity application of desired wavelengths in the application of PhotoDynamic Therapy(PDT) over a broad area. The power sources are varied according to the needs of a specific application. Various attachments and configurations may be used in conjunction with the endoscopic device to enhance performance of a desired application. Such enhancements may include but are not limited to multi–balloon systems for centering the apparatus or limiting the treatment area, fiber optics for directly viewing the area of treatment, vacuum systems for the removal of waste product, delivery tubes for the delivery of aminolevulinic acid (ALA) or other photosensitizers, and other fiber optics for illumination of treatment area. A preferred embodiment of this system for use in PDT employs a multitude of low wattage diodes at the distal end of the endoscope, a scattering glass, cooling channel, external cooling unit, an inflatable balloon with a reflective surface, a tube connected to an external pump for the delivery and removal of photosensitizers. Each diode is selected to emit the respective frequency needed to activate the selected photosensitizer. Alternatively, a range of diodes may be selected to maximize the activation of the photosensitizer. Other embodiments include a double walled balloon fed through a channel of an endoscope which would allow mixing of chemiluminescent chemicals as an

alternative light source within the channel between the balloons. Still other embodiments include different electromagnetic sources for the emission of microwaves or radio frequencies. The prime benefit of this invention is the placement of the electromagnetic radiation source at the distal end of the device to bring the light source directly to the desired site.

The above, and other objects, features and advantages of the present invention will become apparent from the following description read in conjunction with the accompanying drawings.

Brief Description of Figures

Fig. 1 shows a preferred embodiment of an endoscopic device with multiple diodes at the distal end of the device.

Fig. 2 shows a cross section of an endoscopic device with multi-diodes and a center channel.

Fig. 3 shows a double walled balloon endoscopic device for use in chemiluminescent radiation.

Detailed Description of Preferred Embodiments

The present invention provides an endoscopic system, which generates electromagnetic radiation directly at the desired site. Placing the electromagnetic radiation source at the distal end of the endoscopic device allows the device to be placed in an endoscope and moved to the desired site. This configuration has many advantages over prior art whose radiation transmission fiber optic transmission of radiation to a site. The power source to which the fiber is attached creates light in wide dispersion, multi-wavelength, multi-amplitude, and in many axial orientation. Coupling the fiber to the source can be very difficult. The energy being emitted by the laser needs to funneled into the narrow fiber and often this results in a loss of energy. One approach to increasing the efficiency in coupling is seen in U.S. Pat. No. 5,556,267. The core is shaped into a rectangular form to create a larger surface area maximizing the capture area of light. A coupled fiber inherently imposes certain light characteristics in transmitting the light through the fiber and therefore the output light is then limited to those same

characteristics. A fiber depending on the respective refraction indices of the cladding and core allows only certain light to be transmitted through the fiber. The transmitted light will have similar wavelengths, axial orientation, and intensity. Once the light is transmitted, it must be deflected by a diffuser to create diffuse light.

A distally placed source takes full advantage of the emission characteristic of the source as compared to a coupled fiber. A distally placed source such as a diode can have larger numerical aperture (NA), broader dispersion, higher optical efficiency and wider spectrum of radiation as compared to electromagnetic radiation brought through optical fiber.

One type of a source which can be placed at the distal end of a device is a group of laser diode or a pattern of laser diode arrays. Diodes of a specific wavelength are preselected and placed externally at the end of the endoscopic device. The placement of a multitude of diodes at the distal end creates several advantages over standard fiber optics in light quality. The diodes used may be operated at lower wattage because there is no loss due to coupling. With the lower wattage comes the advantages of longer life, greater stability and cooler operation of the diodes. The diodes also have a natural dispersion pattern with one axis spreading more quickly than the other does. An optical fiber by its nature carries a more limited range of light and in the process of coupling to a diode will only output a smaller NA than the diode emits and transmit a smaller portion of energy created by the source. The diode will have a wider dispersion compared to the same light coming from an optical fiber and therefore will not be as prone to the problems with dispersion glass and fiber combination.

An alternative source of electromagnetic radiation in the UV to visible range is chemiluminescence. Through the use of a double walled balloon, chemiluminscent chemicals may be mixed at the distal end of an endoscopic device. The photons emitted from a chemical reaction encompass a broad spectrum.

Yet another alternative source of electromagnetic radiation which can be used in this system is miniature radio frequency or microwave generator. Certain moieties and reactions are activated through the use of energies in these regions.

The present invention is further illustrated by the following examples, but is not limited thereby.

Example 1: An active endoscopic PDT device for mesotetrahydroxyphenylchlorin (mTHPC) treatment of the Esophagus.

A reasonably flexible cylindrical radiation device consists of a body **(101)** on which approximately 150 LED's (with a center line emission of 653 nm) are mounted. The LED emission surfaces **(102)** are protected by a scattering glass**(108)**. An external tube **(103)** blocks undesired wavelengths (example <630 and >670) and defines an annular channel **(104)** to cool the LED's. Coolant **(105)** flows to an external cooler **(106).** The device is powered electronically **(109)** with 30W (30v, 1A). It irradiates with a total useful energy of approximately 200 mW and an extra disposable jacket tube**(107)** is provided. For a fiber tip of 5mm diameter x 5cm length a surface area of approximately 785 sq mm is provided to place diodes on. Diodes at the furthest distal end maybe placed at and angle to increase the area of irradiation even further and provide radiation forward direction.

Example 2: An Active endoscopic PDT Device for the stomach using BenzoPorphyrin Derivatives (BPD) at 682 nm. A laser diode **(204)** of 1W output from its 2 emissions surfaces is grounded on a water-cooled small heatsink and centered and incorporated in an inflatable balloon **(202)(203)** whose outside surface in partially reflective to homogenize the irradiation energy. 2V and 1-2A are sufficient to drive the device. The balloons are fed through a center channel. **(201)** An external expandable sheath may be used for flexibility reasons **(205)**.

Further embodiments of the invention may include devices powered by chemical luminescence microwave and RF.

Example 3: An inflatable double walled balloon is used for irradiating an internal organ.(such as bladders). The space between the inner and outer balloon **(301)** is filled

with chemiluminescence liquid that can be externally replenished. Spent and depleted liquid are externally discharged.

Having described preferred embodiments of the invention with reference to the accompanying drawings, it is to be understood that the invention is not limited to the precise embodiments, and that various changes and modifications may be effected therein by skilled in the art without departing from the scope or spirit of the invention as defined in the appended claims.

What is claimed is:

1. An active endoscopic PhotoDynamic Therapy (PDT) comprising:

   A distal and a proximal end;

   A radiation source positioned at said distal end;

   Wherein said source provides a diffuse radiation pattern across a section of body tissue, which is large compared to said endoscopic device's distal cross section, and which is in proximity to said distal end; and

   Wherein said radiation source is powered remotely and operates at a pre-selected wavelength and power range compatible with requirements of a selected PDT drug.

2. An active endoscopic device according to claim 1, wherein said radiation source is a multitude of diodes mounted on said device's distal end so as to create an illumination pattern to effectively irradiate a selected treatment site.
3. An active endoscopic device according to claim 2, wherein said diodes are diode lasers.
4. An active endoscopic device according to claim 2, wherein said diode lasers comprise lasers operating at different wavelengths.
5. An active endoscopic device according to claim 1, wherein said radiation source is provided by chemiluminescence.
6. An active endoscopic device according to claim 1, further comprising cooling means.
7. An active endoscopic device according to claim 1, further comprising means to deliver a substance which will be activated by said radiation.
8. An active endoscopic device according to claim 1, further comprising means to deliver a substance which will be activated by said radiation.
9. An active endoscopic device according to claim 1, further comprising at least on balloon to serve as a centering mechanism.
10. An active endoscopic device according to claim 9, wherein said homogenizing means is a partially reflective coating on said at least one balloon.

11. A method of performing PhotoDynamic Therapy with an active endoscopic device such as in claim 1, comprising the steps of:

(a) postioning a catheter/endoscope into a patient and directing it to a predetermined treatment site within said patient.

(b) Placing said active endoscopic device into said endoscope/catheter and advancing it so that its distal end with its radiation source are at a distal end of said endoscope; and

(c) Energizing said radiationn source and irradiating said selected treatment site for times and periods to achieve said PDT treatment for said selected treatment sites.

Abstract of the Disclosure

Briefly stated the present invention provides an active endoscopic system which contains an electromagnetic radiation system located at the distal end of the endoscopic device allowing for variable intensity application of desired wavelengths in the application of PhotoDynamic Therapy(PDT) over a broad area. The power sources are varied according to the needs of a specific application. Various attachments and configurations may be used in conjunction with the endoscopic device to enhance performance of a desired application. Such enhancements may include but are not limited to multi–balloon systems for centering the apparatus or limiting the treatment area, fiber optics for directly viewing the area of treatment, vacuum systems for the removal of waste product, delivery tubes for the delivery of aminolevulinic acid (ALA) or other photosensitizers, and other fiber optics for illumination of treatment area. A preferred embodiment of this system for use in PDT employs a multitude of low wattage diodes at the distal end of the endoscope, a scattering glass, cooling channel, external cooling unit, an inflatable balloon with a reflective surface, a tube connected to an external pump for the delivery and removal of photosensitizers. Each diode is selected to emit the respective frequency needed to activate the selected photosensitizer. Alternatively, a range of diodes may be selected to maximize the activation of the photosensitizer. Other embodiments include a double walled balloon fed through a channel of an endoscope which would allow mixing of chemiluminescent chemicals as an alternative light source within the channel between the balloons. Still other embodiments include different electromagnetic sources for the emission of microwaves or radio frequency devices. The prime benefit of this invention is the placement of the electromagnetic radiation source at the distal end of the device to bring the light source directly to the desired site.

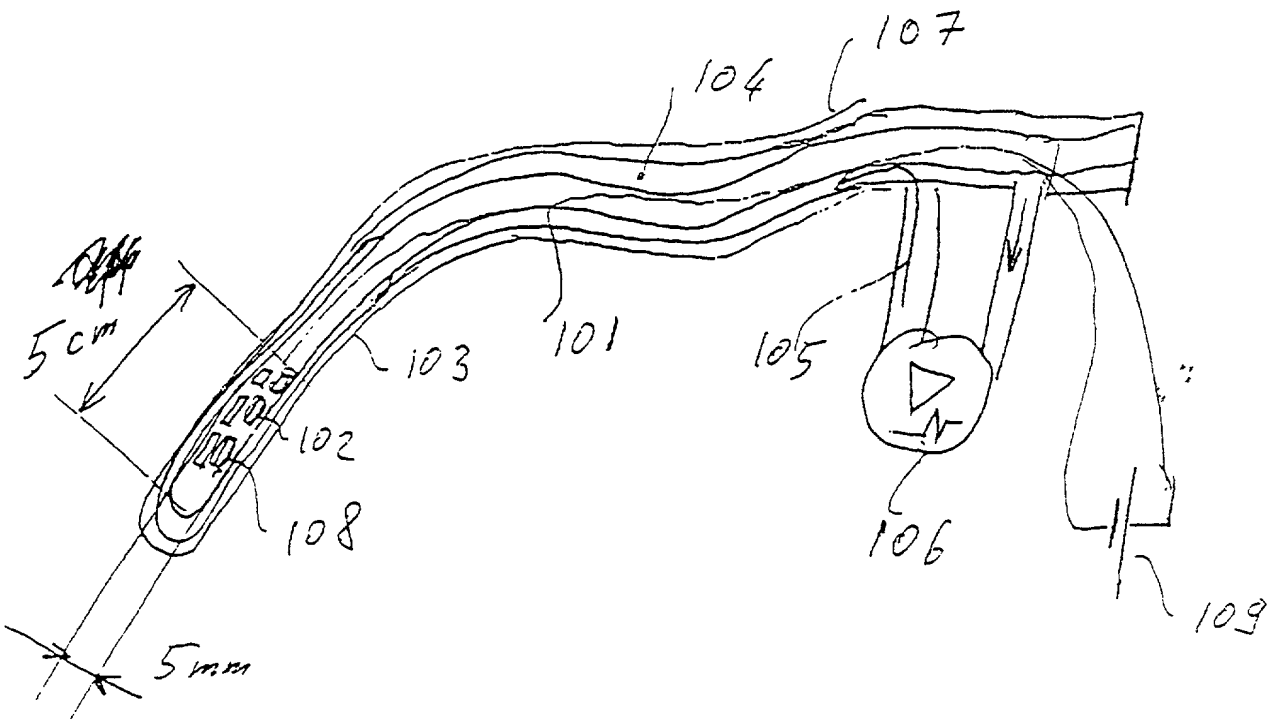

Figure 1

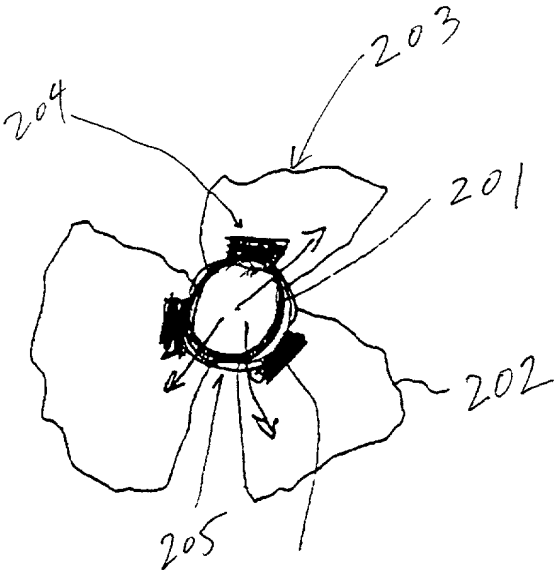

Figure 2

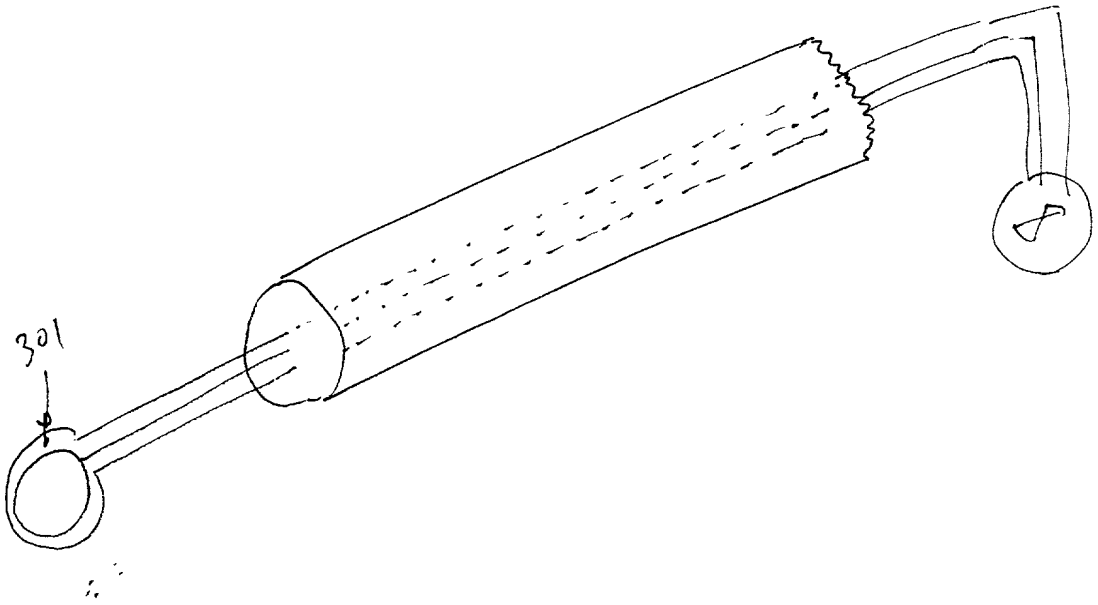

Figure 3

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought for the invention entitled:

TITLE ACTIVE ENDOSCOPIC PHOTODYNAMIC THERAPY DEVICE

the specification, of which is attached hereto, that I have reviewed and understand the contents of the attached specification, including the claims, that I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the inventor's certificate issued before the date of this application filed by me or my legal representatives or assigns more than twelve months prior to this application that I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations 1.56(a) and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows:

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FOREIGN APPLICATIONS FILED MORE THAN 12 MONTHS PRIOR TO THE FILING OF THIS APPLICATION: NONE.

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
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